NEUROTOXICITY AND NEUROPATIC PAIN INDUCED BY BORTEZOMIB: EVALUATION OF PERIPHERAL NERVE FIBRES FROM A CLINICAL TO AN ULTRASTRUCTURAL LEVEL

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AIM: Bortezomib is a proteasome inhibitor compound with a high antineoplastic activity against multiple myeloma and some type of solid tumours. This drug is able to induce a severe peripheral neuropathy and, subsequently, neuropathic pain in the treated patients. In this project, we have developed a rat model of Bortezomib-induced peripheral neuropathy in order to characterize the neuropathic pain induced by this chemotherapy drug. MATHERIALS&METHODS: Bortezomib was administered in Wistar rats at doses of 0.15-0.20mg/kg three times weekly [3q7d] for a total of 8 weeks. At the end of the treatment period, tail sensory nerve conduction velocity (SNCV) was recorded and general toxicity, including haematological parameters, were evaluated. Plantar, Hot Plate and Dynamic Aesthesiometer Tests (Ugo Basile instruments) were used to evaluate the potential insurgence of hyperalgesia and allodynia as a consequence of Bortezomib administration. Sciatic nerves were collected and observed at light and electron microscopy (EM) to observe possible pathological changes in both myelinated and unmyelinated fibres. RESULTS: Bortezomib induced a significant reduction in SNCVs in the treated groups which resulted to be dose-cumulative; the same tendency was also observed in the dynamic aesthesiometer test, indicating the insurgence of allodynia. There was no presence of differences in blood cell and platelet counts in the haematological data. EM examination showed morphological alteration of the unmyelinated fibres in treated nerves when compared to controls, in accordance with dynamic test results; vacuolization of cytoplasm Schwann cells and unmyelinated axons, with loss of microtubule organization, were observed. CONCLUSIONS: In this study, we developed a reliable neuropathic model induced by Bortezomib treatment that can be useful in increasing our knowledge regarding the mechanisms underlying its neurotoxicity.

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